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L2: Entry 30 of 115 File: USPT Nov 6, 2001

DOCUMENT-IDENTIFIER: US 6312693 B1
TITLE: Antibodies against human CD40

Brief Summary Paragraph Right (2):
CD40 is a type I cell surface receptor and a member of the tumor necrosis factor receptor (TNFR) supergene family. Though originally identified as a B cell antigen, CD40 is now believed to be expressed by all antigen presenting cells (APC), including dendritic cells, keratinocytes, and monocytes. CD40 is also expressed by cell types that can act as APC under certain conditions, such as vascular endothelial cells, or cells involved in direct interactions with T cells or T cell precursors such as thymic epithelial cells. More recently, it has also been reported that CD40 can be expressed by fibroblasts, eosinophils, and activated T cells. CD40 expression has also been seen in cancerous cells. Evidence for this is primarily derived from the identification of some carcinoma and melanoma derived cell lines which are CD40.sup.+. (Clark and Ledbetter, Proc. Natl. Acad. Sci. (1986) 83:4494-98; Schriever et al., J. Exp. Med. (1989) 169:2043-58; Caux et al., J. Exp. Med. (1994) 180:1263-72; Alderson et al., J. Exp. Med. (1993) 178:669-74; Young et al., Int. J. Cancer (1989) 43:786-94; Paulie et al., Cancer Immunol. Immunother. (1985) 20:23-28; Denfeld et al., Eur. J. Immunol. (1996) 26:2329-34; Gaspari et al., Eur. J. Immunol. (1996) 26:1371-77; Peguet-Navarro et al., J. Immunol. (1997) 158:144-52; Hollenbaugh et al., J. Exp. Med. (1995) 182:33-40; Galy and Spits, J. Immunol. (1992) 149:775-82; Yellin et al., J. Leukoc. Biol. (1995) 58:209-16; Ohkawara et al., J. Clin. Invest. (1996) 97:1761-66).

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L2: Entry 43 of 115 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6224859 B1
TITLE: Composition containing immature mammalian dendritic cells for enhancing tolerogenicity to foreign graft

Brief Summary Paragraph Right (7):
An example of a thoroughly studied atypical or "deviant" cytokine-modulated immune response induced by bone marrow-derived antigen-presenting cells ("APC") is provided by Streilein et al. (Streilein, et al., J. Neuroimmunol., 39:185 (1992); Wilbanks, et al., J. Immunol., 146:2610 (1991)). Streilein and his colleagues studied class II.sup.dim APC with dendritic morphology, which are now believed to be variant DC in the iris, ciliary body, and other tissues lining the anterior chamber of the eye (Wilbanks, et al., J. Immunol., 146:3018 (1991); Streilein, et al., J. Neuroimmunol., 39:185 (1992)). After APC took up bovine serum albumin ("BSA") injected into the anterior chamber of test specimens, the BSA was presented ineffectively to local T-cells, and subsequently in the spleen when APC-peptide complexes arrived there. As a consequence, the test specimen experienced both a dampened systemic and local, or ocular, immune response when challenged with antigen. Although DC precursors appear to be concentrated in the liver, similar subpopulations presumably exist in all other tissues and whole organs, and particularly in the bone marrow, which constitutes a major source of leukocytes.

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Search Results -

Term	Documents
DENDRITIC.USPT.	4709
DENDRITICS.USPT.	12
PRECURSOR.USPT.	74320
PRECURSORS.USPT.	51185
STEM.USPT.	110678
STEMS.USPT.	34761
ANTIGEN$	0
ANTIGEN.USPT.	36510
ANTIGENA.USPT.	2
ANTIGENADJUVAX.USPT.	1
ANTIGENAEMIA.USPT.	14
((DENDRITIC)SAME (PRECURSOR OR STEM) SAME ANTIGEN$).USPT.	115

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Search: L2

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Search History

DATE: Thursday, June 20, 2002 Printable Copy Create Case

Set Name side by side	**Query**	**Hit Count**	**Set Name** result set
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L2	(dendritic)same (precursor or stem) same antigen$	115	L2
L1	5972627.pn.	1	L1

END OF SEARCH HISTORY

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Search Results -

Term	Documents
FLT3$	0
FLT3.USPT.	79
FLT3L.USPT.	11
FLT3L-TREATED.USPT.	1
"FLT3L.SUP".USPT.	1
"FLT3L.SUP.++".USPT.	1
FLT31.USPT.	2
FLT3-BINDING.USPT.	3
FLT3-EXPRESSING.USPT.	4
FLT3-FC.USPT.	1
FLT3-FLT3-L.USPT.	1
(FLT3$.CLM.).USPT.	21

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Search History

DATE: Thursday, June 20, 2002 Printable Copy Create Case

Set Name side by side	**Query**	**Hit Count**	**Set Name** result set
DB=USPT; PLUR=YES; OP=ADJ			
L7	flt3$.clm.	21	L7
DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L6	flt3$ same dendritic	6	L6
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L5	flt3$ same dendritic.clm.	3	L5
L4	flt3$ same dendritic	49	L4
L3	flt3$ and dendritic	82	L3
L2	L1 and flt3$	1	L2
L1	lynch-david$	47	L1

END OF SEARCH HISTORY

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     $0.29  Estimated cost this search
     $0.29  Estimated total session cost   0.082 DialUnits

File 410:Chronolog(R)  1981-2002/May
       (c) 2002 The Dialog Corporation

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SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R)  1969-2002/Jun W3
         (c) 2002 BIOSIS
  File  73:EMBASE  1974-2002/Jun W3
         (c) 2002 Elsevier Science B.V.
*File  73: For information about Explode feature please
see Help News73.
  File 155:MEDLINE(R)  1966-2002/Jun W2
*File 155: Daily alerts are now available. This file has
been reloaded. Accession numbers have changed.
  File 399:CA SEARCH(R)  1967-2002/UD=13625
         (c) 2002 AMERICAN CHEMICAL SOCIETY
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.

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           86483  DENDRITIC
      S1     674  FLT3? AND DENDRITIC
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...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
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...examined 50 records  (300)
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      S3       0  S2 AND PY=1993
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5/3/1   (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)

10166594   BIOSIS NO.: 199698621512
In vivo administration of **FLT3** ligand but not G-CSF nor GM-CSF results in the generation of large numbers of **dendritic** cells in mice.
AUTHOR: Maraskovsky E; McKenna H J; Brasel K; Tepee M; Roux E; Lyman S D; Williams D E
AUTHOR ADDRESS: Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 86 (10 SUPPL. 1):p423A **1995**
CONFERENCE/MEETING: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

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      S6       8  S2 AND PY=1996
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6/3/1   (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)

10738938   BIOSIS NO.: 199799360083
Dendritic cell development in culture from thymic precursor cells in the absence of granulocyte/macrophage colony-stimulating factor.
AUTHOR: Saunders Dolores; Lucas Karen; Ismaili Jamila; Wu Li; Maraskovsky Eugene; Dunn Ashley; Shortman Ken(a)
AUTHOR ADDRESS: (a)Walter Eliza Hall Inst. Med. Res., PO Royal Melbourne Hosp., Melbourne, VIC 3050**Australia
JOURNAL: Journal of Experimental Medicine 184 (6):p2185-2196 **1996**
ISSN: 0022-1007
RECORD TYPE: Abstract
LANGUAGE: English

6/3/2   (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)

10732931   BIOSIS NO.: 199799354076
Targeted disruption of the **FLT3** ligand gene in mice affects multiple hematopoietic lineages, including natural killer cells B lymphocytes, and **dendritic** cells.
AUTHOR: McKenna H J; Miller R E; Brasel K; Maraskovsky E; Maliszewski C; Pulendran B; Lynch D; Teepe M; Roux E R; Smith J; Williams D E; Lyman S D ; Peschon J J; Stocking K
AUTHOR ADDRESS: Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p474A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971

RECORD TYPE: Citation
LANGUAGE: English

6/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732785 BIOSIS NO.: 199799353930
Flt3 ligand: A novel **dendritic** cell (DC)-stimulating cytokine that induces tumor regression and anti-tumor immune responses in vivo.
AUTHOR: Lynch D H; Andreasen A; Miller R E; Schuh J C L
AUTHOR ADDRESS: Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p437A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10732784 BIOSIS NO.: 199799353929
Distinct function, phenotype and localization of lymphoid and myeloid **dendritic** cell subsets in **FLT3**-L treated mice.
AUTHOR: Pulendran B(a); Lingappa J; Kennedy M(a); Smith J(a); Wright B(a); Teepe M(a); Rudensky A; Williams D E(a); Maliszewski C(a); Maraskovsky E (a)
AUTHOR ADDRESS: (a)Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p437A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10731674 BIOSIS NO.: 199799352819
Administration of **Flt3** ligand results in the generation of large numbers of phenotypically distinct populations of **dendritic** cells in mice.
AUTHOR: Maraskovsky E(a); Brasel K(a); Pulendran B(a); Tepee M(a); Roux E (a); Shortman K D; Lyman S D(a); Williams D E(a); Maliszewski C(a); McKenna H J(a)
AUTHOR ADDRESS: (a)Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p159A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10731673 BIOSIS NO.: 199799352818
The effect of **FLT3** ligand and/or c-kit ligand on the generation of **dendritic** cells from human CD34+ bone marrow.
AUTHOR: Maraskovsky E; Roux E; Tepee M; McKenna H J; Brasel K; Lyman S D; Williams D E
AUTHOR ADDRESS: Immunex Corp., Seattle, WA**USA
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p159A **1996**
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10698320 BIOSIS NO.: 199799319465
Dramatic increase in the numbers of functionally mature **dendritic** cells in **Flt3** ligand-treated mice: Multiple **dendritic** cell subpopulations identified.
AUTHOR: Maraskovsky Eugene(a); Brasel Ken; Teepe Mark; Roux Eileen R; Lyman Stewart D; Shortman Ken; McKenna Hilary J
AUTHOR ADDRESS: (a)Immunex Corporation, 51 University St., Seattle, WA 98101**USA
JOURNAL: Journal of Experimental Medicine 184 (5):p1953-1962 **1996**
ISSN: 0022-1007
RECORD TYPE: Abstract
LANGUAGE: English

6/3/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06704387 EMBASE No: 1996369336
Dramatic increase in the number of functionally mature **dendritic** cells in **Flt3** ligand-treated mice: Multiple **dendritic** cell subpopulations identified
Maraskovsky E.; Brasel K.; Teepe M.; Roux E.R.; Lyman S.D.; Shortman K.; McKenna H.J.
Immunex Corporation, 51 University St.,Seattle, WA 98101 United States
Journal of Experimental Medicine (J. EXP. MED.) (United States) 1996, 184/5 (1953-1962)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
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Search Results -

Term	Documents
FLT3$	0
FLT3.DWPI,EPAB,JPAB.	36
FLT3L.DWPI,EPAB,JPAB.	3
FLT3-BINDING.DWPI,EPAB,JPAB.	1
FLT3-L.DWPI,EPAB,JPAB.	9
FLT3-LIGAND.DWPI,EPAB,JPAB.	10
FLT3/FLK2.DWPI,EPAB,JPAB.	6
FLT3/ITD.DWPI,EPAB,JPAB.	1
DENDRITIC.DWPI,EPAB,JPAB.	2180
DENDRITICS.DWPI,EPAB,JPAB.	2
(FLT3$ SAME DENDRITIC).JPAB,EPAB,DWPI.	6
(FLT3$ SAME DENDRITIC).JPAB,EPAB,DWPI.	6

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Search: L6

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Search History

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DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L6	flt3$ same dendritic	6	L6
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L5	flt3$ same dendritic.clm.	3	L5
L4	flt3$ same dendritic	49	L4
L3	flt3$ and dendritic	82	L3
L2	L1 and flt3$	1	L2
L1	lynch-david$	47	L1

END OF SEARCH HISTORY

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L3: Entry 62 of 82 File: USPT Aug 28, 2001

DOCUMENT-IDENTIFIER: US 6280724 B1
TITLE: Composition and method for preserving progenitor cells

Detailed Description Paragraph Right (43):
The type of cells generated in methylcellulose colony assays in cultures containing 50 ng/mL of the cytokine cocktail (FIG. 4) was determined by flow cytometry. These data are summarized in FIG. 5. Sca.sup.+ cells were greatly increased in pylartin-containing cultures; other cell surface markers were not particularly affected. The Sca antigen is expressed on murine stem cells and other mature cells including T cells. In this experiment, T cells (CD3) were not increased. FIG. 5 shows a flow cytometric analysis of the cell surface phenotype of cells harvested from cells cultured in 50 ng/mL of early-acting recombinant murine cytokines (mIL1, mIL3, mKL) (BioSource International, Camarillo, Calif.), in the presence and absence of pylartin samples, prior to colony assay (far right bars from FIG. 4). Pylartin-RK generated 14.5-fold more Sca-1 cells than medium control. Sca-1, or Ly6, is an antigen associated with primitive murine progenitors and also mature blood cells including T cells, etc. (Spangrude et al. 1991). No differences were observed in the numbers of T cells (CD3), dendritic cells (CD11b), or cells expressing the Fc-gamma receptor (e.g., granulocytes and monocytes), CD38, or the transferrin receptor (CD71) (antibodies obtained from Pharmigen, Calif.).

Detailed Description Paragraph Type 0 (7):
Hannum, C O et al., "Ligand for Flt3/fk2 receptor tyrosine kinase regulates growth of hematopoietic stem cells and is encoded by variant RNAs," Nature 368:643 (1994).

Detailed Description Paragraph Type 0 (8):
Lyman, S D et al., "Molecular cloning of a ligand for the Flt3/flk2 tyrosine kinase receptor: a proliferative assay for primitive hematopoietic cells," Cell 75:1157 (1993).

Detailed Description Paragraph Type 0 (12):
Shah, A J et al., "flt3 Ligand induces proliferation of quiescent human bone marrow CD34.sup.+ CD38.sup.- cells and maintains progenitor cells in vitro," Blood, 87:3563-3570 (1996). Sharon, N, and H Lis, "Lectins as cell recognition molecules," Science, 246:227-234 (1989).

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L3: Entry 69 of 82 File: USPT Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165785 A
TITLE: Bone marrow cultures for developing suppressor and stimulator cells for research and therapeutic applications

Brief Summary Paragraph Right (23):
The present invention also relates to methods of inducing at least partial tolerance to an antigen comprising the steps of administering to the recipient animal a tolerogenic amount of a dendritic cell population, and administering to the recipient animal a tolerogenic amount of a suppressor cell population, substantially contemporaneously with the dendritic cell population. The antigen may be an alloantigen, autoantigen, or xenoantigen.

Brief Summary Paragraph Right (43):
The suppressor effect may be concentrated by PERCOLL fractionation and further enriched by FACS (fluorescence antibody cell sorter) sorting of the "nonlymphocyte" region of this fraction. In stark contrast to fraction 3, cells isolated in fraction 4 are highly stimulatory. On light microscopy the fraction 3 cells appeared as highly activated foamy macrophages. The FACS signature of this cell population is bland, with few positive markers noted in the active region of fraction 3. Specifically, the cell is not a lymphocyte, showing no staining for CD, CD4, CD8 or the rat pan-T cell clone OX-52. The cells are positive for a rat macrophage antigen marker (clone R2-1A6A) and we found significant staining with the antibody clone OX-33 (marking for CD45RA) in these cells as well. This cell bears little similarity to veto cells, dendritic cells, facilitator cells, progenitor cells, or some of the previously described natural suppressor cells, but appears to be a highly suppressive macrophage derived from the conditions of the co-culture.

Brief Summary Paragraph Right (54):
Supplemental Factors: Specific supplementation with colony stimulating factors is necessary. The current technique utilizes species specific granulocyte macrophage-colony stimulating factor (GM-CSF). Where species specific factor is unavailable (i.e., the rat) murine GM-CSF is used and a concentration of 100 units/mL is added at the start of the culture. Additional agents for the stimulation and maturation of cells are added. The current model employs lipopolysaccharide (LPS or bacterial endotoxin) obtained from E coli and added at 1 .mu.g/mL at the start of the culture. Additional growth/factors that may be used in addition or in place of GM-CSF include macrophage colony stimulating factor ("M-CSF"), granulocyte-colony stimulating factor ("G-CSF") and the FLT3 ligand. Additional stimulating factors that may be added or used in place of LPS include interluekin-6, interleukin-4, tumor necrosis factor alpha ("TNF.alpha."), and transforming growth factor beta ("TGF.beta. "). Again, all factors used are species specific unless unavailable, in which case either murine or human factors can be employed.

Brief Summary Paragraph Right (74):
At present, deleterious immune reactions are prevented or treated by general immune suppression in that the suppression is not antigen specific. Nonspecific immune suppression agents, such as steroids and antibodies to lymphocytes, put the host at increased risk for infection and development of tumors. In recent years, unwanted immune reactions have been prevented or treated with more selective immune suppression, such as with Cyclosporine A (CsA). CsA was thought to inhibit the proliferation of cytotoxic T cells while having relatively little effect on the proliferation of suppressor T cells. In addition, immunosuppressive therapy with CsA leads to depletion of the thymic medullary dendritic cells, the principal antigen

presenting cells of the adult thymus. Although CsA has significantly improved the overall success of transplants and has shown some success with autoimmune diseases, it must be administered for the life of the patient. As a result, patients receiving such long-term CsA therapy are constantly at considerable risk for infections and neoplasms, as well as toxicity from the CsA.

Brief Summary Paragraph Right (76):
Therefore, in another embodiment of the present invention, it is possible to separately culture donor specific dendritic cells while, in parallel, culturing suppressor cells in separate media. In this embodiment, dendritic cells and suppressor cells are grown according to methods well known in the art.

Brief Summary Paragraph Right (80):
In this alternate embodiment, the present invention provides methods of inducing at least partial tolerance to an antigen comprising the steps of administering to the recipient animal a tolerogenic amount of a dendritic cell population; and administering to the recipient animal a tolerogenic amount of a suppressor cell population, substantially contemporaneously with the dendritic cell population. The antigen may be an alloantigen, autoantigen, or xenoantigen.

Brief Summary Paragraph Right (81):
In yet another embodiment, the present invention includes a method of inducing at least partial tolerance to an antigen comprising the steps of administering to the recipient animal a tolerogenic amount of a dendritic cell population; administering to the recipient animal a tolerogenic amount of a suppressor cell population, substantially contemporaneously with the dendritic cell population; and administering an immunosuppressive agent for a time and under conditions sufficient to induce allograft tolerance wherein the immunosuppressive agent is administered substantially contemporaneously with the administration of dendritic cells and suppressor cells of the present methods. The antigen may be an alloantigen, autoantigen, or xenoantigen.

Brief Summary Paragraph Right (83):
Dendritic cells ("DC") may be obtained from one of the sources known in the art by known methods. Typically, the cells are obtained from the bone marrow, blood, liver, fetal liver, or the spleen or may be obtained by differentiating bone marrow progenitor cells.

Brief Summary Paragraph Right (92):
The two separate cell cultures (dendritic cells and suppressor cells) may be propagated for about 1 day to about 21 days and are preferably propagated from about 2 days to about 10 days and most preferably for about 7 days. Typically, the cells will be propagated for about the same length of time. However, one type could be grown for a different length of time. At the end of the propagation phase, the dendritic and suppressor cells are recovered and delivered to a host.

Brief Summary Paragraph Right (93):
It is contemplated that target cells will be located within an animal or human patient, in which case a safe and effective amount of the therapeutic cells, in pharmacologically acceptable form, would be administered to the patient. Generally speaking, it is contemplated that useful methods of the present invention will include the selected cells in a convenient amount, e.g., from about 1.times.10.sup.6 total cells/kg body weight to about 1.times.10.sup.9 total cells/kg body weight of the dendritic and suppressor cell mix, administered at a dosage of about 1.times.10.sup.5 total cells/kg body weight to about 1.times.10.sup.8 total cells/kg body weight of the dendritic and suppressor cell mix.

Brief Summary Paragraph Right (94):
Typically, the two populations of cells will be mixed prior to administration to a host but may be administered separately to the host. The cells are preferably administered in a ratio from about 2:1 to about 1:20 dendritic cells:suppressor cells. The cells are more preferably administered in a ratio of from about 1:1 to about 1:10 dendritic cells:suppressor cells.

Brief Summary Paragraph Right (104):

The methods of the invention also comprise administering, to a host, an enriched dendritic cell population in combination with an enriched suppressor cell population suspended in a pharmaceutically-acceptable carrier.

Brief Summary Paragraph Right (105):
As used herein, the term "enriched" as applied to the cell populations of the invention refers to a more homogeneous population of dendritic or suppressor cells which have fewer other cells with which they are naturally associated. An enriched population of cells can be achieved by several methods known in the art. For example, an enriched population of dendritic cells can be obtained using immunoaffinity chromatography using monoclonal antibodies specific for determinants found only on dendritic cells.

Brief Summary Paragraph Right (107):
Monoclonal antibodies against antigens specific for mature, differentiated cells have been used in a variety of negative selection strategies to remove undesired cells, for example, to deplete T cells or malignant cells from allogeneic or autologous marrow grafts, respectively (Gee, et al., J.N.C.I. 80:154, 1988). Purification of human hematopoietic cells by negative selection with monoclonal antibodies and immunomagnetic microspheres can be accomplished using multiple monoclonal antibodies (Griffin, et al., Blood, 63:904, 1984). Enriched dendritic cell composition can be obtained from a mixture of lymphocytes, since dendritic cells lack surface Ig or T cell markers and do not respond to B or T cell mitogens in vitro. Dendritic cells also fail to react with MAC-1 monoclonal antibodies, which reacts with all macrophages. Therefore, MAC-1 antibodies provide a means of negative selection for dendritic cells.

Brief Summary Paragraph Right (109):
The immunosuppressive agent used according to the method of the invention is an agent that decreases the host's immune response to antigens. A preferred immunosuppressant of the invention is Cyclosporine A (CsA), however other agents, which cause immune suppression by depletion of thymic medulla dendritic cells, such as rapamycin, desoxyspergualine, and FK506 or functional equivalents of these compounds, may also be utilized. CsA is preferably administered by injection at a dose from about 0.3 to about 50 mg/kg/day, preferably from about 2.5 mg/kg/day to about 10 mg/kg/day. The duration of CsA treatment may range from about two to about 20 days, preferably about 14 days.

Brief Summary Paragraph Right (111):
As used herein, "substantially contemporaneously" refers to the time at which each of the therapeutic cells or immunosuppressant is administered to the recipient in relation to the time at which the others are administered. For example, a heart transplant recipient may receive enriched dendritic cells derived from donor spleen, during transplant surgery and receive CsA for a short time immediately following for about 10-16 days, preferably about 14 days. In general, where transplant grafts are involved, the immunosuppressive agent can be administered from about one day to about 90 days before infusion of the tolerogenic cells until about seven days to about 90 days after the infusion of tolerogenic cells. Preferably, the immunosuppressive agent is administered from about seven days to about 28 days before infusion of tolerogenic cells until about seven days to about 28 days after infusion of tolerogenic cells. Where autoimmune disease is treated by infusion of foreign or altered tolerogenic cells, administration of immunosuppressive agent parallels the treatment times described for transplant grafts.

Brief Summary Paragraph Right (112):
According to the invention, an allogeneic bone marrow transplant recipient may have his own bone marrow harvested and processed to obtain a composition of enriched dendritic cells before transplantation of the donor bone marrow. The patient may receive immunosuppressive therapy followed by the infusion of transplanted bone marrow and dendritic cell composition previously harvested from the patient's own bone marrow.

Brief Summary Paragraph Right (114):
In an additional aspect, the present invention is directed to various methods of utilizing the cell mix produced by the present invention for therapeutic and/or

diagnostic purposes. For example, the mix of dendritic cells and suppressor cells may find use in: (1) regenerating tissues which have been damaged through acute injury, abnormal genetic expression or acquired disease; (2) treating a host with damaged tissue by removal of small aliquots of bone marrow, differentiating them in vitro, isolating the desired subpopulation of differentiated cells and re-introducing the differentiated cells back into the host (3) detecting and evaluating growth factors relevant to the immune system; (4) detecting and evaluating inhibitory factors which modulate the immune system.

Brief Summary Paragraph Right (118):
Supplemental Factors: Specific supplementation with colony stimulating factors is necessary. The current technique utilizes species specific granulocyte macrophage-colony stimulating factor (GM-CSF). Where species specific factor is unavailable (i.e. the rat) murine GM-CSF is used and a concentration of 100 units/mL is added at the start of the culture. Additional agents for the stimulation and maturation of cells are added. The current model employs lipopolysaccharide (LPS or bacterial endotoxin) obtained from E coli and added at 1 .mu.g/mL at the start of the culture. Additional growth/factors that may be used in addition or in place of GM-CSF include macrophage colony stimulating factor ("M-CSF"), granulocyte-colony stimulating factor ("G-CSF") and the FLT3 ligand. Additional stimulating factors that may be added or used in place of LPS include interleukin-6, interleukin-4, tumor necrosis factor alpha ("TNF.alpha."), and transforming growth factor beta ("TGF.beta."). Again, all factors used are species specific unless unavailable, in which case either murine or human factors can be employed.

CLAIMS:

1. A method of treatment comprising the steps of:

(a) obtaining stem cells from bone marrow;

(b) combining the stem cells with splenocytes to form a co-culture;

(c) adding a first factor selected from the group consisting of lipopolysaccharide, interleukin-6, interleukin-4, tumor necrosis factor alpha, transforming growth factor beta, anti-CD3 and mixtures thereof to the co-culture;

(d) adding a second factor selected from the group consisting of granulocyte macrophage colony-stimulating factor, macrophage-colony stimulating factor, granulocyte-colony stimulating factor, FLT3 ligand and mixtures thereof to the co-culture;

(e) maintaining the co-culture for at least 4 days;

(f) obtaining differentiated immune system suppressor cells and immune system stimulator cells from the co-culture; and

(g) introducing the immune system suppressor cells and immune system stimulatory cells into a host;

wherein the immune system suppressor cells are capable of prolonging allograft survival when infused as a donor specific transfusion to a transplant patient.

10. A method of reducing the amounts of general immunosuppressive drugs given to a transplant patient, comprising the steps of:

a) removing bone marrow;

b) obtaining a first population of cells from the bone marrow, wherein the first population of cells are stem cells;

c) combining the stem cells with a second cell population derived from lymphoid tissue to produce a co-culture;

d) adding granulocyte macrophage-colony stimulating factor and lipopolysaccharide to

the co-culture;

e) allowing the stem cells to differentiate;

f) obtaining immune system suppressor cells from the co-culture;

g) administering to a transplant patient the immune system suppressor cells and a third population of cells, wherein the third population of cells are dendritic cells selected from the group consisting of dendritic cells of splenic, bone marrow, blood, liver and fetal liver origin, and mixtures thereof;

wherein the immune system suppressor cells are capable of prolonging graft survival in the transplant patient.

11. A method according to claim 10, wherein the immune system suppressor cells and the dendritic cells are administered to a transplant patient as a donor specific transfusion in a dendritic cell:suppressor cell ratio of from about 2:1 to about 1:20.

13. A method according to claim 10, wherein the dendritic cells are derived from spleen cells.

14. A method according to claim 10, wherein the transplant patient receives immune system suppressor cells and dendritic cells in an amount of from about 1.times.10.sup.6 to about 1.times.10.sup.9 total cells per kilogram body weight.

17. A method of treatment comprising the steps of:

a) obtaining stem cells from bone marrow;

b) combining the stem cells with splenocytes in medium to form a co-culture;

c) adding to the medium granulocyte macrophage-colony stimulating factor at a level of 100 units/ml medium, and lipopolysaccharide at a level of 1 .mu.g/ml medium;

d) maintaining the co-culture for from 4 to 14 days;

e) obtaining differentiated immune system suppressor cells from the co-culture;

f) introducing the immune system suppressor cells into a host; and

g) substantially contemporaneously introducing an enriched population splenic of dendritic cells into the host;

wherein the immune system suppressor cells are capable of prolonging allograft survival when infused as a donor specific transfusion to a transplant patient.

18. A method according to claim 17, wherein the immune system suppressor cells and the splenic dendritic cells are administered to the host in a ratio of from about 2:1 to about 1:20.

20. A method according to claim 19, wherein the host receives of a total of immune system suppressor cells and splenic dendritic cells of from about 1.times.10.sup.6 to 10.times.10.sup.9 total cells/Kg body weight.